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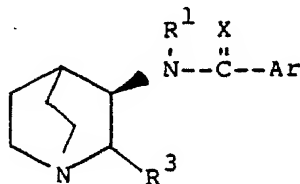
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(54) Anxiolytic-R-N-(1-azabicyclo[2.2.2]oct-3-yl) benzamides and thiobenzamides.

(57) Compounds of general formula I



(I)

EP 0 311 724 A1

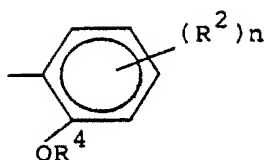
wherein

X represents oxygen or sulphur;

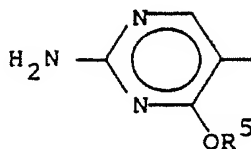
each of R<sup>1</sup> and R<sup>3</sup> independently represents hydrogen or a C<sub>1</sub>-C<sub>4</sub> alkyl group;

Ar represents:

a phenyl ring optionally substituted by one, two or three C<sub>1</sub>-C<sub>4</sub> alkoxy groups and/or by one or two halogen atoms;  
a phenyl ring of the general formula



wherein  $R^2$  represents halogen, 4,5-benzo, C<sub>1</sub>-C<sub>8</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl or Am, wherein Am represents amino, methylamino or dimethylamino,  
 $R^4$  represents C<sub>1</sub>-C<sub>8</sub> alkyl,  
n is 1 or 2; or  
a pyrimidinyl moiety of the general formula



wherein  $R^5$  is C<sub>1</sub>-C<sub>4</sub> alkyl;

and their N-oxides and pharmaceutically acceptable salts are useful as anxiolytic agents. A preferred compound is R-(+)-4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide.

ANXIOLYTIC-R-N-(1-AZABICYCLO[2.2.2]OCT-3-YL) BENZAMIDES AND THIOMBENZAMIDES

The present invention relates to certain optical isomers of N-(3-quinuclidinyl)benzamides and thiobenzamides, namely R-N-(3-quinuclidinyl)-benzamides and thiobenzamides, otherwise known as R-N-(1-azabicyclo[2.2.2]oct-3-yl)-benzamides and thiobenzamides, which have been observed to exhibit anxiolytic (antianxiety) properties in warm blooded animals.

Quinuclidine analogues of sulpiride were prepared and studied by Mikhlin, E. E. et al as reported in Khim-Farmatsevt. Zh. 10, No. 11, 56-60 (1976); C.A. 85: 155489r exemplified by the compound: 5-aminosulphonyl-N-(1-azabicyclo[2.2.2]oct-3-yl)-2-methoxybenzamide. This compound and others in the series were reported by the authors not to have antiemetic activity. The above named compound was reported in USSR Patent SU-A-414261 to have neuroleptic activity.

Syntheses of 4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)benzamide and N-(1-azabicyclo[2.2.2]oct-3-yl)-benzamide were reported by Mikhlin, E. E. et al in Khim-Farmatsevt. Zh. 7, 20-24 (1974); C.A. 79, 146458a and the latter in Khim.Geterosikl. Soedin., Akad. Nauk. Latv. SSR 243-9 (1966); C.A. 65: 2220b. These compounds were reported to exhibit hypotensive, narcotic and ganglionic stimulation and blocking activities.

Synthesis of 4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-3-chloro-5-trifluoromethylbenzamide was reported in DE-A- 2548968; C.A. 87, 68001c and in equivalently related US-A-4093734 from 4-amino-3-chloro-5-trifluoromethyl benzoic acid chloride and 3-aminoquinuclidine. The compound is in a class among pyrrolidinyl and piperidinyl benzamides which are said to be useful as anxiolytics, anticonvulsives, antiemetics and antiulcerogenics.

It is widely recognized that substituted benzamides are a class of drugs known to be effective in psychiatry and gastroenterology (Sulpiride and other Benzamides; International Workshop on Sulpiride and other benzamides, Florence, Feb. 17-18 (1978), Raven Press]. However, the R-N-(1-azabicyclo[2.2.2]oct-3-yl)-benzamides used in this invention have now been found to have marked anxiolytic properties.

EP-A-0099789 and FR-A-2529548 disclose racemic mixtures of N-(1-azabicyclo[2.2.2]oct-3-yl) benzamides and their use as gastrointestinal motility accelerators.

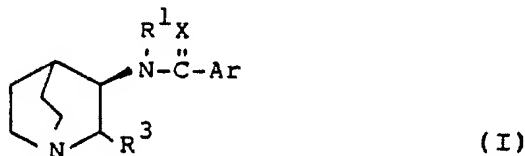
US-A-4593034 and EP-A-0158532 disclose the treatment of emesis caused by the administration of platinum anticancer drugs (such as cisplatin) by the use of racemic mixtures of 2-alkoxy-N-(1-azabicyclo[2.2.2]oct-3-yl) benzamides or thiobenzamides.

EP-A-0201165 describes a large class of compounds, covering certain racemic mixtures of N-(1-azabicyclo[2.2.2]oct-3-yl) benzamides and reports that they are useful in the treatment of emesis, anxiety and/or irritable bowel syndrome (IBS).

FR-A0-8701355 (filed 4th February 1987) discloses that S-enantiomers of the compounds disclosed in EP-A-0099789 increase the motility of certain areas of the gastrointestinal tract and inhibit emesis, particularly that induced by cisplatin.

It has now unexpectedly been discovered that the R-enantiomers of various N-(1-azabicyclo[2.2.2]oct-3-yl)benzamides exhibit anxiolytic activity in warm blooded animals. This is in complete contrast to the earlier observation that S-enantiomers of N-(1-azabicyclo[2.2.2]oct-3-yl)benzamides were more active in the gastrointestinal activity, referred to above.

According to a first aspect of the present invention, there is provided a compound of general formula I



wherein:

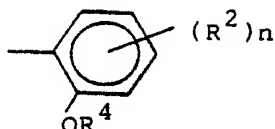
X represents oxygen or sulphur;

each of R<sup>1</sup> and R<sup>3</sup> independently represents hydrogen or a C<sub>1</sub>-C<sub>4</sub> alkyl group;

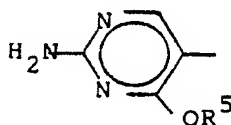
Ar represents:

a phenyl ring optionally substituted by one, two or three C<sub>1</sub>-C<sub>4</sub> alkoxy groups and/or by one or two

halogen atoms;  
a phenyl ring of the general formula



10 wherein  $R^2$  represents halogen, 4,5-benzo,  $C_1$ - $C_8$  alkoxy,  $C_1$ - $C_4$  alkylcarbonyl or Am, wherein Am represents amino, methylamino or dimethylamino,  
 $R^4$  represents  $C_1$ - $C_8$  alkyl,  
 n is 1 or 2; or  
 15 a pyrimidinyl moiety of the general formula



wherein  $R^5$  is  $C_1$ - $C_4$  alkyl;

25 or an N-oxide and/or pharmaceutically acceptable salt thereof. The compound will generally be substantially free of the  $S$ -enantiomer.

Preferred compounds of the invention include those having one or more of the following features:

- each of  $R^1$  and  $R^3$  independently represents hydrogen, methyl or ethyl
- Ar represents 4-Am-5-chloro-2-methoxyphenyl.

30 A particularly preferred compound of the invention is  $R$ -(+)-4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide whether as the free base or a salt (for example fumarate or hydrochloride).

In the further definition of symbols in the formulae hereof and where they appear elsewhere throughout this specification and the claims, terms have the following significance.

35 The term " $C_1$ - $C_8$ alkyl" as used herein includes straight and branched chain radicals of up to eight carbons inclusive and is exemplified by such groups as methyl, ethyl, propyl, isopropyl, butyl, amyl, hexyl, heptyl, and octyl radicals and the like. The term " $C_1$ - $C_8$ alkoxyl" has the formula  $-O-C_1-C_8$ alkyl. The terms " $C_1$ - $C_4$ alkyl" and " $C_1$ - $C_4$ alkoxyl" are to be construed as containing up to four carbon atoms accordingly.

40 The terms "halo" or "halogen" when referred to herein include fluorine, chlorine, bromine and iodine unless otherwise stated. Chlorine and bromine are preferred. "Pharmaceutically acceptable salts" include the acid addition salts, hydrates, alcoholates and salts of the compounds, which salts are physiologically compatible in warm blooded animals. The acid addition salts may be formed by either strong or weak acids. Representative of strong acids are hydrochloric, sulphuric and phosphoric acids. Representative of weak acids are fumaric, maleic, succinic, oxalic, citric, tartaric, cyclohexamic and the like.

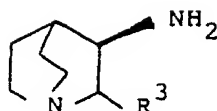
45 Protected amino groups used in synthesis are acetylamino or benzoylamino radicals and the like on the benzamide moiety mentioned hereinbelow in synthetic methods.

The optically active compounds (which term includes salts where the context so admits) of the first aspect of the invention may broadly speaking be prepared either by separation from racemates or other mixtures with the corresponding  $S$ -enantiomer or by asymmetric synthesis. According to a second aspect of the present invention, there is therefore provided a process for the preparation of a compound of general formula I, the process comprising either

- (1) separating a compound of general formula I from a mixture with its corresponding  $S$ -enantiomer;

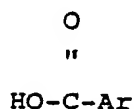
or

- (2.1.1) coupling a 3-aminoquinuclidine of absolute configuration  $R$  of general formula (II)



(II)

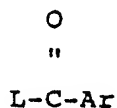
wherein R<sup>3</sup> is as defined for general formula (I) with an acid of general formula (III):



(III)

wherein Ar is as defined for general formula (I); or

(2.1.2) reacting an R-3-aminoquinuclidine of general formula (II) with an acid derivative of general formula (IIIa)



(IIIa)

wherein Ar is as defined for general formula (I) and L is a leaving group; and

(2.1.3) optionally after step 2.1.1 or 2.1.2 converting a compound of general formula (I) so formed in which X represents an oxygen atom into a compound of general formula (I) in which X represents a sulphur atom; or

(2.2) when X represents a sulphur atom reacting an R-3-aminoquinuclidine of general formula (II) with an aldehyde ArCHO wherein Ar is as defined for general formula (I) and sulphur; or

(2.3) for an amino-substituted compound of general formula (I) reducing a corresponding nitro-substituted compound, and

(2.4) optionally after any of steps 1, 2.1.1, 2.1.2, 2.1.3, 2.2 and 2.3 converting a compound of general formula (I) so formed into another compound of general formula (I) or an N-oxide and/or salt thereof.

N-oxides can be prepared by treatment with a peracid such as m-chloroperbenzoic acid or hydrogen peroxide in an organic solvent such as methylene chloride at room temperature. Salts can be prepared as described above.

Process (1) may be achieved for example by recrystallisation of a salt formed with an optically active acid (for example an enantiomer of tartaric acid). By way of illustration, the following protocol may be followed for the resolution of N-(3-quinuclidinyl)-3-chlorobenzamide (N-(1-azabicyclo[2.2.2]oct-3-yl)-3-chlorobenzamide).

To the racemate in base form is added a solution of dextrorotatory L tartaric acid in methanol. The mixture obtained is brought to reflux, filtered when hot and left to cool. The precipitate is filtered and redissolved in boiling methanol. After cooling and filtration, the precipitate is dissolved in boiling methanol again. After cooling and filtration, the compound obtained is dissolved in water; the resulting aqueous solution is basified by means of sodium carbonate, extracted with chloroform, dried on sodium sulphate and filtered. The filtrate is evaporated. The product obtained is dissolved in acetone and hydrochloric ethanol (about 6N) is added; the precipitate obtained is filtered and recrystallized in ethanol. Thus, the dextrorotatory isomer is obtained.

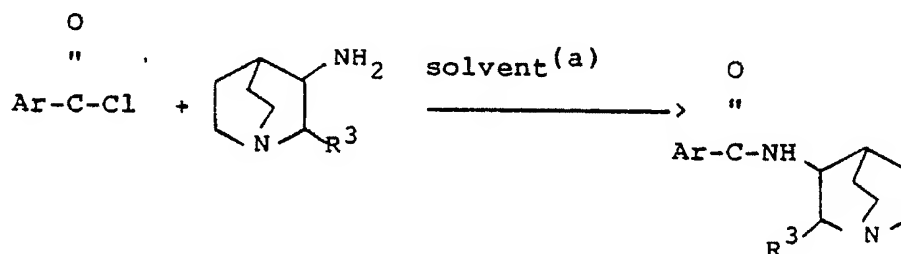
The mother liquor of the first three recrystallizations in methanol and combined and evaporated. The residue is taken in water, and the resulting mixture is basified by means of sodium carbonate and then extracted with chloroform. The extract is dried on sodium or magnesium sulphate and filtered. The filtrate is evaporated. To the product is added a solution of laevorotatory D-tartaric acid in methanol. The mixture is brought to reflux, filtered when hot and the filtrate is cooled. The precipitate obtained is then filtered. This precipitate is dissolved in boiling methanol and the solution is filtered when hot. After the filtrate has cooled, the precipitate obtained is filtered. A precipitate is obtained which is dissolved in water. The solution is basified by means of sodium carbonate, extracted with chloroform and the extract is dried on sodium or

magnesium sulphate. It is then filtered and the filtrate is then evaporated leaving a residue which is dissolved in acetone and hydrochloric ethanol (about 6N). The precipitate obtained is filtered and recrystallized in ethanol. In this way, the laevorotatory isomer is obtained.

### Preparation of Benzamides

Racemates of compounds of Formula I and the corresponding R- or S-isomers are preparable by reacting a suitably activated benzoic acid derivative with 3-aminoquinuclidine to form the corresponding benzamide under a variety of conditions. Two general methods, A and B, are illustrated in the following equations:

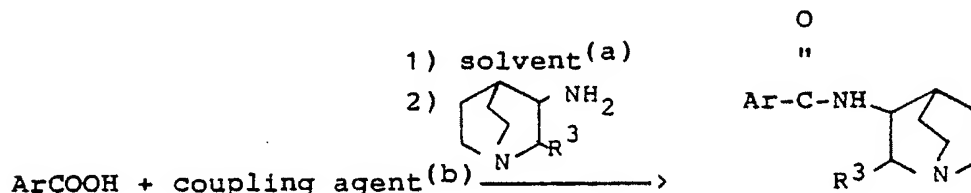
#### Method A, using an Acid Chloride



(a) Suitable solvents are organic solvents or a mixture of organic solvents and water; examples of organic solvents include chloroform and diethyl ether.

Method A is illustrated by Examples 5, 6, 7 and 9.

#### Method B, using a coupling agent



(a) e.g., tetrahydrofuran

(b) e.g., dicyclohexylcarbodiimide or 1,1'-carbonyldiimidazole

Method B is illustrated in Examples 1, 3 and 8 and 14.

Compounds wherein  $R_2$  is primary amino may also be prepared from a compound prepared by Methods A or B, wherein  $R_2$  is nitro by catalytic reduction of the nitro compound.

Alternatively, compounds wherein  $R_2$  is amino may be prepared by procedures of Method A utilizing a starting benzoyl halide wherein the amino group has been protected, or they may be prepared from compounds prepared in Method A or B wherein  $R_2$  is nitro and reducing the nitro radical to an amino radical.

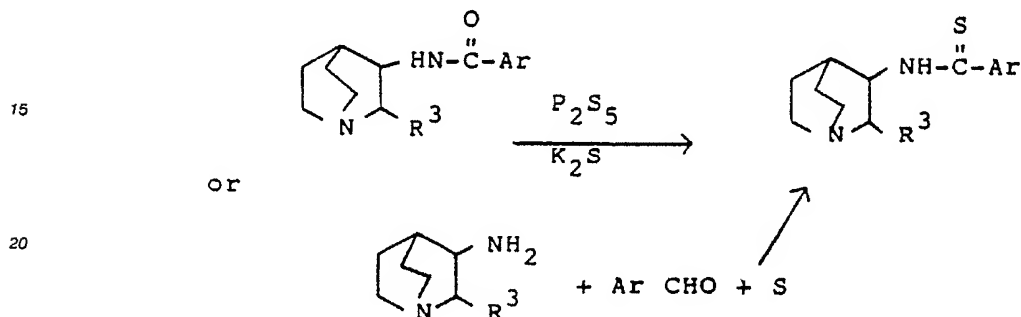
Preferably, the compounds wherein  $R_2$  is amino or methylamino are prepared by Method B.

The free base of any compound of Formula I from its acid addition salt may be regenerated by usual

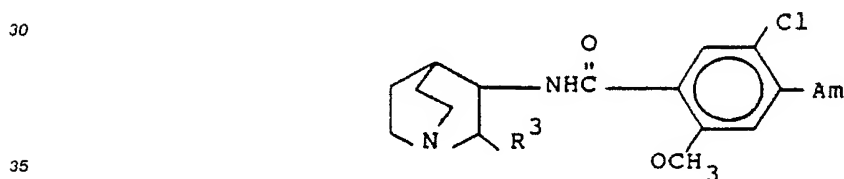
procedures of partitioning between dilute aqueous base and a suitable solvent, separating the solvent layer, drying and evaporating.

## 5 Preparation of Thiobenzamides

The preparation of the thiobenzamido compounds of Formula I' may be accomplished by mixing and reacting a benzamido compound of Formula I with a mixture of phosphorus pentasulphide ( $P_2S_5$ ) and potassium sulphide ( $K_2S$ ) or by mixing and reacting 3-aminoquinuclidine with an appropriately substituted benzaldehyde and sulphur. The reaction sequences are illustrated by the following:



25 In these methods, compounds wherein  $R_2$  is nitro may be reduced to compounds wherein  $R_2$  is amino. A preferred group of compounds encompassed by Formula I have the formula:



wherein Am is amino (i.e.,  $-NH_2$ ) or methylamino. As will be recognized from the above description, these compounds (Ic) are preferably prepared by Method B.

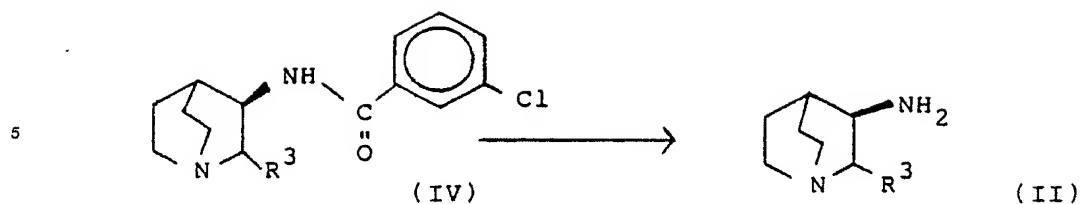
40 In process step 2.1.1 the coupling may be effected by means of a carbodiimide such as dicyclohexylcarbodiimide or 1,1'-carbonyldiimidazole.

In process step 2.1.2 the leaving group L may be a halogen atom (such as chlorine) in which case the compound of general formula (IIa) will be an acid halide.

45 In process step 2.1.3 the conversion of a compound of general formula (I) where X is an oxygen atom to a compound of general formula (I) where X is a sulphur atom may be effected by mixing and reacting with a mixture of phosphorus pentasulphide and potassium sulphide.

An R-3-aminoquinuclidine of general formula (II) may be prepared by a number of different ways as follows. Although the following description is given primarily with reference to the case when  $R^3$  is hydrogen (that is, when the 3-aminoquinuclidine moiety is otherwise unsubstituted), it is to be understood that it is 50 equally applicable to cases where  $R^3$  is an alkyl radical. Compounds of general formula (II) can be prepared by the reduction of the oxime of the corresponding 3-quinuclidinone by treatment with hydrogen and Raney nickel. The oximes in turn are preparable by treatment of the corresponding 3-quinuclidinones with hydroxylamine hydrochloride in the presence of base. The 2-alkyl-3-quinuclidinones can be prepared by reduction with palladium-on-carbon; their production is described in J. Het. Chem. 3 109 (1966).

55 First, a compound of general formula (II) may be obtained by hydrolysing an optionally substituted benzamide such as an R-N-(3-quinuclidinyl)-3-chlorobenzamide of general formula (IV):

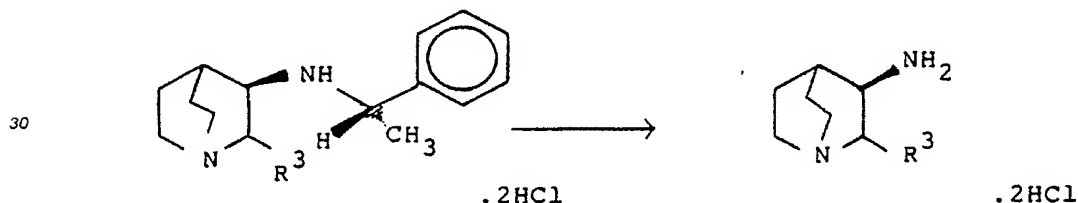


10 Hydrolysis may be achieved by dilute acid, such as dilute hydrochloric acid, in which case the dihydrochloride salt of compound (II) will result.

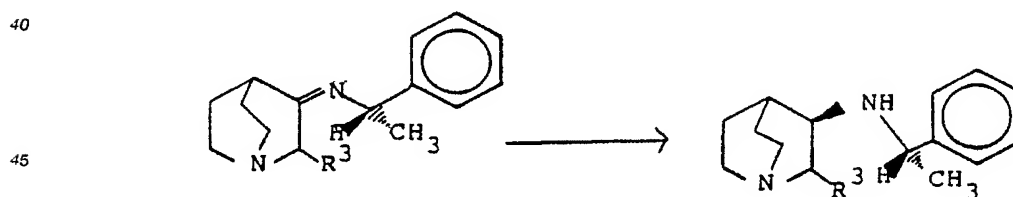
R-N-(3-quinuclidinyl)-3-chlorobenzamides of general formula (IV) may be separated from a racemic mixture by crystallization of the diastereoisomeric salts obtained by the action of L-tartaric acid. Treatment of the appropriately separated salt with base yields the free R-N-(3-quinuclidinyl)-3-chlorobenzamide.

15 A racemic mixture of R- and S-N-(3-quinuclidinyl)-3-chlorobenzamides may be obtained by condensing a racemic 3-aminoquinuclidine with a reactive derivative of 3-chlorobenzoic acid or with 3-chlorobenzoic acid itself and a coupling agent such as a carbodiimide. Racemic 3-aminoquinuclidines may be obtained by the action of hydroxylamine or hydrochloride followed by base (such as sodium ethoxide) on 3-quinuclidinones and reduction of the corresponding oxime with hydrogen and Raney nickel, as an example.

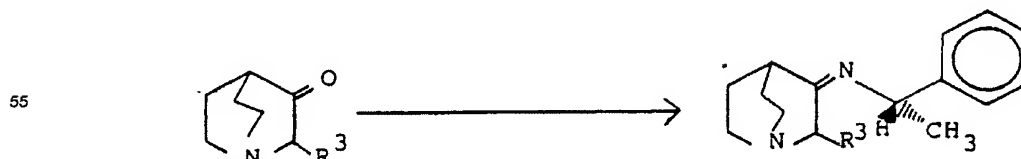
20 If necessary 3-quinuclidinones may be prepared by oxidising 3-quinuclidinols, whose preparation is described in *J. Am. Chem. Soc.* 74, 2215 (1952). Secondly, a compound of general formula (II) may be produced by debenzylating S-N-(alpha-methylbenzyl)-R-3-aminoquinuclidine by hydrogenolysis in an acid medium in the presence of a catalyst such as palladium on carbon.



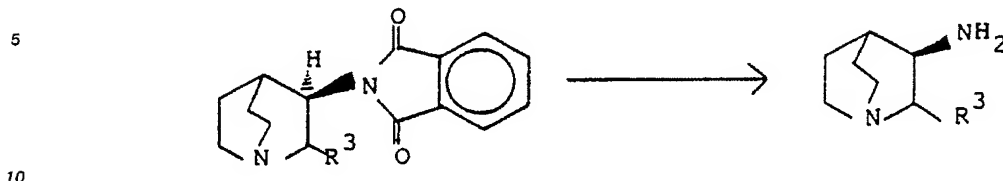
35 S-N-(alpha-methylbenzyl)-R-3-aminoquinuclidine may be obtained by the reduction of S-N-(alpha-methylbenzyl)-3-quinuclidinimine by hydrogenolysis in the presence of a catalyst such as platinum oxide or by a borohydride such as potassium borohydride.



50 In turn, the S-N-(alpha-methylbenzyl)-3-quinuclidinimine may be obtained by treating 3-quinuclidinone with S-alpha-methylbenzylamine.



Thirdly, R-3-aminoquinuclidine may be prepared, as the dichloride, from R-phthalimido-3-quinuclidine by treating the starting material with hydrazine and then with hydrochloric acid.



In turn, R-phthalimido-3-quinuclidine can be obtained from S-3-quinuclidinol, which is known from Eur. J. Med Chem (1979) 14, 111-114, by reacting the alcohol with phthalimide in the presence of triphenylphosphine and ethyl azodicarboxylate.



The mechanism of this reaction involves an inversion of configuration of the hydroxy-bearing carbon atom (J. Am. Chem Soc (1972) 84, 679).

According to a third aspect of the present invention, there is provided a compound of general formula I for use in pharmaceutical and/or veterinary medicine, particularly in the treatment of anxiety.

According to a fourth aspect of the invention, there is provided a pharmaceutical and/or veterinary composition comprising (a) a compound of general formula I and (b) a suitable carrier therefor.

According to a fifth aspect of the invention, there is provided the use of a compound of general formula I in the preparation of an anxiolytic agent.

The anxiolytic activity was determined by the method of Costall et al details of which are to be found in the pharmacology examples later in this specification. In brief, the method involves seeing whether the compound under test reduced the natural anxiety of mice in brightly-lit areas. Anxiolytic activity was also assessed by the method of Crawley and Goodwin (Pharm. Biochem. Behavior (1980), 13,167-170).

It is therefore a primary object to provide R-N-(1-azabicyclo[2.2.2]oct-3-yl)benzamides and thiobenzamides.

A further object is to provide R-N-(1-azabicyclo[2.2.2]oct-3-yl)benzamides and thiobenzamides having anti-anxiety properties.

A still further object is to provide means for controlling anxiety.

The invention will now be illustrated by the following non-limiting examples.

#### EXAMPLE 1

R(+)-4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide, fumarate [1:1].

R(+)-4-Amino-5-chloro-2-methoxy-N-(quinuclidin-3-yl)benzamide, fumarate [1:1].

In a closed system equipped with an oil bubbler, 30ml of tetrahydrofuran was added to a mixture of 4-amino-5-chloro-2-methoxybenzoic acid, 2.02g, (0.010 mole) and 1,1'-carbonyldiimidazole, 1.62g (0.010 mole) with stirring. When evolution of carbon dioxide ceased, nitrogen was bubbled through the reaction mixture for 1 hr. A solution of 3-aminoquinuclidine, 1.26g, (0.010 mole) in 10ml tetrahydrofuran was added dropwise to the stirred reaction mixture and stirring at room temperature continued for 3 hrs. TLC analysis (3% conc. ammonium hydroxide solution in methanol) showed some product formation. The mixture was

heated at reflux temperature for 18 hours and then concentrated to an oil. TLC analysis showed the presence of the product, imidazole, and 3-aminoquinuclidine. The oil was dissolved in methylene chloride (75ml) and washed twice with 50ml portions of aqueous sodium bicarbonate solution. The methylene chloride layer was dried over anhydrous magnesium sulphate and concentrated to yield 2.0g (67%) of a glassy amorphous solid, the free base of the title compound.

In another reaction on a 0.020 mole scale, 5.18g (83.8%) of the product as the free base was obtained.

The products were combined, dissolved in methanol (20ml) and the solution and treated with a solution of fumaric acid (2.73g) in methanol (50ml). Absolute ether was added to precipitate the salt which was collected by filtration and recrystallized from methanol-water (200:20) with isopropyl ether added to the point of incipient cloudiness. The recrystallized salt (5.38g) melted at 223-225 °C.

Analysis:

Calculated for  $C_{13}H_{24}N_3O_6Cl$ :

C,53.59; H,5.68; N,9.89

Found :

C,53.35; H,5.72; N,9.95

From the racemate, the R(+) isomer and the S(-) isomer are separated.

## EXAMPLE 2

R(+) -4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide, hydrochloride, hydrate (1:1:1).

(R(+) -4-Amino)-5-chloro-2-methoxy-N-(quinuclidin-3-yl)benzamide, hydrochloride, hydrate (1:1:1).

To an isopropyl alcohol solution of the free base of the title compound such as was obtained by the procedure of Example 1 is added an equal molar amount of 37% (conc.) hydrochloric acid. The crude salt is separated by filtration and recrystallized from acetone-water to give the title compound, m.p. 158-160 °C. From the racemate, the R(+) isomer is separated.

## EXAMPLE 3

R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxy-4-(methylamino)benzamide, fumarate [1:1].

R-5-chloro-2-methoxy-4-methylamino-N-(quinuclidin-3-yl)benzamide, fumarate [1:1].

To a mixture of 1,1'-carbonyldiimidazole, 1.23g (0.00756 mole) and 5-chloro-2-methoxy-4-methylaminobenzoic acid, 1.63g (0.00756 mole) was added 50 ml of tetrahydrofuran. Nitrogen was bubbled into the solution for 30 minutes to remove any carbon dioxide that was present. To the solution was added 3-aminoquinuclidine, 0.95g, (0.00756 mole) in one portion, and the reaction mixture was stirred at ambient temperature for 16 hours. The reaction mixture was concentrated to an oil which was shown to be 1:1 mixture of the free base of the product and imidazole. The mixture was dissolved in 20ml methanol and treated with a solution containing 0.47g fumaric acid in 20ml of hot methanol. Upon cooling, 1.52g of white solid formed. Recrystallization from water-methanol gave 0.84g of the product as a white solid; m.p. 237-238 °C.

Analysis:

Calculated for  $C_{20}H_{26}N_3O_6Cl$ :

C,54.61; H,5.96; N,9.55

Found :

C,54.61; H,5.98; N,9.51

From the racemate, the R isomer is separated.

#### EXAMPLE 4

R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxy-4-(methylamino)-benzamide, hydrochloride (1:1).

10 (R-5-chloro-2-methoxy-4-(methylamino)-N-(quinuclidin-3-yl)benzamide, hydrochloride (1:1).

To an isopropyl alcohol solution of the free base of the title compound, such as was obtained by the procedure of Example 3, is added an equal molar amount of 37% (conc.) hydrochloric acid. The crude salt is separated by filtration and recrystallized from ethanol-water to give the title compound, m.p. 255-258° C.

15 From the racemate, the R isomer is separated.

#### EXAMPLE 5

20 R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-2-methoxybenzamide, fumarate [1:1]hemihydrate.

(R-2-methoxy-N-(quinuclidin-3-yl)benzamide, fumarate [1:1]hemihydrate).

25 In a closed system equipped with an oil bubbler, a solution of 2-methoxybenzoyl chloride, 2.76g (0.0016 mole) in 50ml absolute ether was added dropwise over 10 min to a stirred solution of 3-aminoquinuclidine, 1.81g (0.0144 mole) in 100ml absolute ether. After the addition was completed, the mixture was stirred at room temperature for an additional 2 hrs. The solid hydrochloride salt was collected by filtration under  
30 nitrogen. The salt (3.83g) was dissolved in sodium bicarbonate solution and extracted twice with 25ml portions of methylene chloride. The extract was dried over magnesium sulphate and concentrated to yield 1.25g clear oil (33.3%). TLC analysis (3% conc. ammonium hydroxide in methanol) showed the free base to be pure. A solution of 1.17g of the free base in 5ml methanol was treated with a solution of 0.52g fumaric acid in 10ml methanol. Isopropyl ether was added to give approximately 100ml of solution from which the  
35 fumarate salt precipitated. The salt was collected under nitrogen and dried in a vacuum oven at 60° C overnight. NMR and elemental analyses showed that the product was a hemihydrate.

Analysis:

Calculated for  $C_{19}H_{25}N_2O_{6.5}$ :

C, 59.21; H, 6.54; N, 7.27

40 Found:

C, 59.18; H, 6.30 N, 7.25

From the racemate, the R isomer is separated.

#### 45 EXAMPLE 6

R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-2,4-dimethoxybenzamide hydrochloride [1:1].

50 (R-N-(quinuclidinyl-3-yl)-2,4-dimethoxybenzamide hydrochloride [1:1].

A mixture of 3-aminoquinuclidine dihydrochloride, 6.95g, (0.0349), 2,4-dimethoxybenzoyl chloride, 700g, (0.0349 mole), anhydrous sodium carbonate, 36.99g, (0.349 mole), 175ml water, and 175ml chloroform was  
55 stirred rapidly to achieve good mixing of the 2 layers for 20 hrs. The chloroform layer was then separated, washed with water, dried over anhydrous magnesium sulphate, and concentrated to an impure oil. The oil was triturated twice with 20ml portions of petroleum ether to remove some impurities. The oil was then dissolved in ether and filtered to remove a small amount of insoluble material. The filtrate was treated with

ethereal hydrogen chloride and the resulting salt collected to yield 2.70g (23.7% yield) white solid. The salt was recrystallized from ethanol-isopropyl ether. Further recrystallization from methanol-ethyl ether yielded a white solid, m.p. 211-212° C. The NMR analysis was satisfactory.

Analysis:

5 Calculated for  $C_{16}H_{23}N_2O_3Cl$ :

C,58.80; H,7.09; N,8.57

Found :

C,58.38; H,7.13; N,8.44

From the racemate, the R isomer is separated.

10

#### EXAMPLE 7

15 R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-2,4-dimethoxybenzamide, sulphate[1:].

(R-2,4-dimethoxy-N-(quinuclidin-3-yl)benzamide, sulphate[1:]).

20 In a closed system equipped with an oil bubbler, a solution of 2,4-dimethoxybenzoyl chloride, 13.08g, (0.0652 mole) in 200ml absolute ether was added dropwise over 30 minutes to a stirred solution of 3-aminoquinuclidine, 7.80g, (0.0619 mole) in 200ml absolute ether. The mixture was stirred overnight, and the solid hydrochloride salt of the product was filtered under nitrogen. The material was dried in a vacuum oven at 40° C to give 18.70g (92%). A 2.94g (0.009 mole) portion of the hydrochloride salt in 20ml methanol was  
25 treated with a solution of sodium methoxide prepared from 0.23g (0.010 mole) sodium metal and 10ml methanol. After standing a few minutes, the mixture was filtered and the filtrate concentrated on a rotary evaporator, and the residue was triturated with 75ml methylene chloride. After filtering to remove some insoluble solids, the filtrate was concentrated to yield 2.53g of the free base of the title compound (97% recovery from the hydrochloride salt). The free base was dissolved in 100ml acetone and concentrated  
30 sulphuric acid (0.483ml) added dropwise with stirring. The solid that formed was collected under nitrogen to give 2.76g of the salt which recrystallized from methanol-isopropyl ether and dried in a vacuum oven at 60° C for 2 hrs and then overnight at 78° C; m.p. 223-225° C.

Analysis:

Calculated for  $C_{16}H_{24}N_2O_7S$ :

35 C,49.47; H,6.23; N,7.23

Found :

C,49.41; H,6.30; N,7.25

From the racemate, the R isomer is separated.

40

#### EXAMPLE 8

45 R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-2,4-dimethoxybenzamide, fumarate [1:1.5].

(R-2,4-dimethoxy-N-(quinuclidin-3-yl)benzamide, fumarate [1:1.5]).

50 In a closed system equipped with an oil bubbler, tetrahydrofuran, 100ml, was added to a mixture of 2,4-dimethoxybenzoic acid, 3.64g (0.020 mole) and 1,1'-carbonyldiimidazole, 3.24g (0.020 mole). No evolution of carbon dioxide was observed and after stirring for 3 hrs, TLC (ethyl acetate) and mass spectral analysis showed that the starting material had reacted to form N-(2,4-dimethoxybenzoyl)imidazole and imidazole. A solution of 3-aminoquinuclidine, 2.52g (0.020 mole) in 10ml tetrahydrofuran was added to the mixture, and the solution was heated to reflux temperature for 1 hr and then allowed to stand overnight at room  
55 temperature. A solution of fumaric acid, 2.32g (0.020 mole) in 50ml methanol was added to the reaction mixture. Tetrahydrofuran was added until the solution became slightly turbid. The solution was chilled in a refrigerator. The solid which precipitated from solution was collected by filtration and found to be a fumarate salt of 3-aminoquinuclidine. The filtrate was concentrated to an oil and triturated with tetrahydrofuran. The

- solid precipitate which formed on standing was filtered and shown by TLC (3% concentrated ammonium hydroxide in methanol) to be the desired product plus traces of imidazole and 3-aminoquinuclidine. Recrystallization from methanol-isopropyl ether gave 5.41g white crystalline solid (67% yield calculated as the monofumarate). NMR and elemental analysis showed the salt to contain less than one equivalent of fumaric acid. The salt was dissolved in boiling methanol (50ml) and treated with an additional 0.77g (0.0066 mole) fumaric acid in 10ml hot methanol. Isopropyl ether was added until the hot solution became turbid. The solid obtained on cooling was collected, recrystallized from methanol-isopropyl ether and dried in a vacuum oven at 78 °C overnight. NMR and elemental analysis showed the salt to be a 1.5 fumarate, m.p. 192-192.5 °C.
- Analysis:  
 Calculated for  $C_{22}H_{28}N_2O_9$ :  
 C,56.89; H,6.08; N,6.03  
 Found :  
 C,56.81; H,6.13; N,6.04
- From the racemate, the R isomer is separated.

EXAMPLE 9

- R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-2-propoxybenzamide hydrochloride [1:1].

(R-2-propoxy-N-(quinuclidin-3-yl)benzamide hydrochloride [1:1].

- To a solution of 3.82g (0.0192 mole) of 3-aminoquinuclidine dihydrochloride in about 25ml of carbon dioxide-free water was added 8g (0.025 mole) of barium hydroxide octahydrate. The mixture was warmed for 5 minutes and then dried to a powder on a rotary evaporator. While protecting from contamination with carbon dioxide in the atmosphere, the powder was extracted in sequence with hot benzene and a 1:1 mixture of benzene-methylene chloride solution. The combined extracts were dried over magnesium sulphate and the mixture filtered. To the filtrate with agitation was added dropwise a solution of 3.4g (0.0171 mole) of 2-propoxybenzoyl chloride in 50ml of methylene chloride. The mixture was warmed on a steam bath to evaporate about 75% of the methylene chloride. Ligroin (60-110) was added and the mixture solidified. The solid was recrystallized from anhydrous ethyl alcohol to give 3.9g (62.0%), m.p. 210-211 °C.
- Analysis:  
 Calculated for  $C_{17}H_{25}N_2O_2Cl$ :  
 C,62.86; H,7.75; N,8.62  
 Found :  
 C,62.62; H,7.59; N,8.54
- From the racemate, the R isomer is separated.

EXAMPLE 10

- R-N-(1-Azabicyclo[2.2.2]oct-3-yl)-3-methoxy-2-naphthalene-carboxamide, hydrochloride [1:1].

(R-3-methoxy-2-naphthalene-N-(quinuclidin-3-yl)carboxamide, hydrochloride [1:1]).

- A solution of 1.69g (0.00768 mole) of 3-methoxy-2-naphthoic acid chloride in 15ml of methylene chloride was added dropwise to a stirred solution of 0.97g (0.00768 mole) of 3-aminoquinuclidine in 25ml of methylene chloride in a closed system equipped with an oil bubbler. The reaction mixture was stirred overnight at ambient temperature, and then concentrated to give an off-white glassy solid. Two recrystallizations from methanol-isopropyl ether gave 1.95g (73.4%) of the product as an off-white solid which was vacuum dried at ambient temperature, m.p. 248-252 °C.
- analysis:  
 Calculated for  $C_{19}H_{23}N_2O_2Cl$ :

C.65.79; H.6.68; N.8.08

Found :

C.65.40; H.6.72; N.8.01

From the racemate, the R isomer is separated.

#### EXAMPLE 11

10 R-4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxythiobenzamide fumarate.

(R-4-Amino-5-chloro-2-methoxy-N-(quinuclidin-3-yl)thiobenzamide fumarate).

15 One half mole of 4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide fumarate is partitioned between dilute sodium hydroxide and 400ml of benzene. The benzene solution is dried with sodium sulphate and distilled to a volume of 250ml. To this is added a finely-ground mixture of 9g of phosphorous pentasulphide and 9g of potassium sulphide. The mixture is refluxed for 4 hr and an additional 9g of phosphorous pentasulphide is added and reflux continued for 2 hr. The benzene is decanted off. The solid  
20 is dissolved in a suitable solvent and reacted with fumaric acid to give the title compound. From the racemate the 3-R isomers are separated.

#### EXAMPLE 12

25

R-4-Amino-N-(1-aza-2-methylbicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide, fumarate [1:1]

30 (R-4-Amino-5-chloro-2-methoxy-N-(2-methylquinuclidin-3-yl)benzamide, fumarate [1:1])

Following the general procedure of Example 1, but instead of the 3-aminoquinuclidine, using 0.010 moles of 3-amino-2-methylquinuclidine, the title compound was prepared. From the racemate, the 3-R isomers were separated.

35

#### EXAMPLE 13

40 R-4-Amino-N-(1-aza-2-methylbicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide, hydrochloride, hydrate (1:1:1)

R-4-Amino-5-chloro-2-methoxy-N-(2-methylquinuclidin-3-yl)benzamide, hydrochloride, hydrate (1:1:1)

45

To an isopropyl alcohol solution of the free base of the title compound such as was obtained by the procedure of Example 1 is added an equal molar amount of 37% (conc.) hydrochloric acid. The crude salt is separated by filtration and recrystallised from acetone-water to give the title compound. From the racemate, the 3-R isomers were separated.

50

#### PREPARATION 1

55 R( + )-3-aminoquinuclidine, dihydrochloride

(R( + )-1-azabicyclo[2.2.2]oct-3-ylamine, dihydrochloride)

(a) Preparation of R(+)-N-(3-quinuclidinyl)-3-chlorobenzamide, hydrochloride (R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide, hydrochloride)

N-(3-quinuclidinyl)-3-chlorobenzamide (52.5 g) in solution in methanol is added to a solution of L-tartaric acid (29.7 g) in methanol. The precipitate obtained is recovered by filtration and treated twice with methanol at reflux. The salt thus purified is decomposed by an aqueous caustic soda solution and the product extracted with chloroform. After drying and evaporation of the organic phase the base obtained is treated in acetone with an ethanolic hydrochloric acid solution. The hydrochloride which precipitates is recovered by filtration and recrystallised from ethanol. 9.4 g of optically pure R(+)-N-(3-quinuclidinyl)-3-chlorobenzamide, hydrochloride (R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide, hydrochloride) are obtained.

Melting point: 244° - 247° C.  
 $[\alpha]_D^{20} = +16.9^\circ$  (c = 1, CH<sub>3</sub>OH)

(b) Preparation of R(+)-3-aminoquinuclidine, dihydrochloride (R(+)-1-azabicyclo[2.2.2]oct-3-ylamine, dihydrochloride)

The hydrochloride obtained in the preceding step (9 g) is treated with concentrated hydrochloric acid at reflux for 3 hours 30 minutes. The reaction mixture is treated with absolute alcohol and the R(+)-3-aminoquinuclidine, dihydrochloride (R(+)-1-azabicyclo[2.2.2]oct-3-ylamine, dihydrochloride) which crystallises is recovered by filtration.

Melting point: >260° C  
 $[\alpha]_D^{20} = +24.8^\circ$  (c = 1, H<sub>2</sub>O)

## PREPARATION 2

R(+)-3-aminoquinuclidine, dihydrochloride

R(+)-1-azabicyclo[2.2.2]oct-3-ylamine, dihydrochloride

(a) Preparation of S(-)-N-(alpha-methylbenzyl)-3-quinuclidinimine

3-Quinuclidinone (80 g) in 800 ml toluene was refluxed in the presence of S-alpha-methylbenzylamine (77.4 g) for 24 hours, the water formed being eliminated by means of a Dean-Stark trap. The reaction mixture is then concentrated to dryness and the resulting imine (130 g) is distilled.

Yield: 89%  
 Boiling point: 140° - 150° C (0.05 mm Hg)  
 $[\alpha]_D^{20} = -98.6^\circ$  (c = 1, CHCl<sub>3</sub>)

(b) Preparation of S-N-(alpha-methylbenzyl)-R-3-aminoquinuclidine, dihydrochloride

The imine (129.5 g) obtained in the preceding step is dissolved in methanol and potassium borohydride (30.6 g) is added in small portions at between 10° and 20° C. After one hour the mixture is evaporated to dryness under reduced pressure. The residue is dissolved in a mixture of acetone and isopropyl alcohol (2:1). The expected amine is precipitated in the form of the dihydrochloride by the addition of an ethanolic hydrogen chloride solution. The product is recrystallised twice in an ethanol/methanol mixture (1:1) to yield optically pure S-N-(alpha-methylbenzyl)-R-3-aminoquinuclidine, dihydrochloride (81 g).

Yield: 47%

Melting point  $>260^{\circ}\text{C}$   
 $[\alpha]_{\text{D}}^{20} = +1.8$  (2,  $\text{H}_2\text{O}$ )

- 5 (c) Preparation of R(+)-3-aminoquinuclidine, dihydrochloride (R(+)-1-azabicyclo[2.2.2]oct-3-ylamine, dihydrochloride)

The product obtained in the preceding step (64.4 g) is dissolved in ethanol with 2 equivalents of a solution of hydrochloric acid (1 N) and palladium on carbon, 50%  $\text{H}_2\text{O}$  (12.8 g). The reaction mixture is  
 10 stirred for 18 hours under a hydrogen atmosphere, filtered then evaporated to dryness under reduced pressure. R(+)-3-aminoquinuclidine, dihydrochloride is crystallised in an ethanol:ether (1:1) mixture.

$[\alpha]_{\text{D}}^{20} = +24.4$  (1,  $\text{H}_2\text{O}$ )

15 PREPARATION 3

R(+)-3-aminoquinuclidine, dihydrochloride

20

(R(+)-1-azabicyclo[2.2.2]oct-3-ylamine, dihydrochloride)

- 25 (a) R(-)-3-phthalimidoquinuclidine

S(+)-3-quinuclidinol (13.4 g: 0.105 mole), triphenylphosphine (30.4 g: 0.115 mole) and phthalimide (15.7 g: 0.106 mole) are suspended in anhydrous THF (100 ml) at  $0^{\circ}\text{C}$ . Ethyl azodicarboxylate (17.7 ml: 0.115 mole) is added. After returning to ambient temperature, the solution is agitated for 2 hours. The  
 30 solvent is evaporated, the reaction mixture taken up in ethyl acetate and the organic phase is extracted by an aqueous solution of hydrochloric acid (1 N). After washing with ethyl acetate, the aqueous phase is neutralised with  $\text{NaHCO}_3$  and the product is extracted with chloroform. After drying and evaporation of the organic phase, the residue is crystallised in a mixture of petroleum ether and isopropyl ether, to give 19.3 g (72%) R-3-phthalimidoquinuclidine.

35

(b) R(+)-3-aminoquinuclidine, dihydrochloride (R(+)-1-azabicyclo[2.2.2]oct-3-ylamine, dihydrochloride)

The phthalimide obtained in step (a) (14.5 g: 0.056 mole) is refluxed in 200 ml ethanol in the presence  
 40 of hydrazine hydrate (3.1 g: 0.062 mole) for 1 hour 30 minutes. Insoluble matter is removed by filtration and the ethanol is removed under vacuum. The residue is taken up in diethyl ether and the fresh insoluble matter eliminated by filtration. After evaporation of the ether, R(+)-3-aminoquinuclidine dihydrochloride (10.5 g: 72%) is crystallised by a solution of hydrochloric acid in ethanol.

45 Melting point:  $>260^{\circ}\text{C}$   
 $[\alpha]_{\text{D}}^{20} = +24.4$  (c = 1,  $\text{H}_2\text{O}$ )

50 COMPARISON PREPARATION 1

S(-)-3-aminoquinuclidine, dihydrochloride

- 55 (S(-)-1-azabicyclo[2.2.2]oct-3-ylamine, dihydrochloride)

Following the procedure of Preparation 1, but using instead D-tartaric acid, the corresponding S enantiomer was obtained.

Melting point:  $>260^{\circ}\text{C}$   
 $[\alpha]_{\text{D}}^{20} = -24.9^{\circ}$  ( $c = 1$ ,  $\text{H}_2\text{O}$ )

5

## COMPARISON PREPARATION 2

S(-)-3-aminoquinuclidine, dihydrochloride

10

(S(-)-1-azabicyclo[2.2.2]oct-3-ylamine, dihydrochloride)

Following the procedure of Preparation 2, but using instead R-N-alpha-methylbenzylamine, the corresponding S enantiomer was obtained.

15

Melting point:  $>260^{\circ}\text{C}$   
 $[\alpha]_{\text{D}}^{20} = -24.2^{\circ}$  ( $c = 1$ ,  $\text{H}_2\text{O}$ )

20

## EXAMPLE 14

R(+) -4-Amino-N-(3-quinuclidinyl)-5-chloro-2-methoxybenzamide hydrochloride

25

(R(+) -4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide hydrochloride)

R(+)-3-aminoquinuclidine dihydrochloride (40 g; 0.2 mole) is dissolved in an aqueous caustic soda solution (2.5 N). To this solution, cooled in an ice bath, is added 4-amino-5-chloro-2-methoxy benzoic acid (44.5 g) in solution in 300 ml of pyridine. Dicyclohexylcarbodiimide (85 g) is added in two portions. The mixture is vigorously stirred for 18 hours at ambient temperature. The medium is then diluted with 150 ml of water. Insoluble matter is removed by filtration and washed with water. The aqueous phase is brought to pH 10 by a 10 N solution of caustic soda and extracted by chloroform. After drying (over  $\text{Na}_2\text{SO}_4$ ) and evaporation of the organic phase, the residue is crystallised in isopropyl ether.

35

The solid thus obtained (56 g) is dissolved in 280 ml isopropyl alcohol and the solution acidified by 5 N HCl. The hydrochloride which precipitates is recovered by filtration and recrystallised in 99% ethanol. The target product is obtained with a yield of 60%.

40 Melting point:  $232-234^{\circ}\text{C}$   $[\alpha]_{\text{D}}^{20} = +3.8^{\circ}$  ( $c = 1$ ,  $\text{H}_2\text{O}$ )

## COMPARISON EXAMPLE 1

45

S(-)-4-Amino-N-(3-quinuclidinyl)-5-chloro-2-methoxybenzamide hydrochloride

(S(-)-4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide hydrochloride)

50

Following the procedure of Example 14 but using instead S(-)-3-aminoquinuclidine as prepared in Comparison Preparation 1 or 2, the corresponding S enantiomer is obtained.

55 Melting point:  $233-235^{\circ}\text{C}$   
 $[\alpha]_{\text{D}}^{20} = -3.9^{\circ}$  ( $c = 1$ ,  $\text{H}_2\text{O}$ )

## EXAMPLE 15

R(+) -4-Amino-N-(3-quinuclidinyl)-5-chloro-2-methoxybenzamide hydrochloride(R(+)-4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide hydrochloride)

5

R(+)-3-aminoquinuclidine (1.9 g) is dissolved in 33.5 ml of an aqueous 1 N caustic soda solution. To this solution is added drop by drop 4-acetamido-5-chloro-2-methoxybenzoyl chloride (3.75 g) in solution in 70 ml dioxane. After 15 minutes stirring, the reaction medium is acidified, washed with chloroform, basified with a concentrated aqueous caustic soda solution and the product extracted with chloroform. The organic phase is dried (over sodium sulphate) and then evaporated. The oily residue is dissolved in ethanol and ethanol/HCl is added to an acid pH. The 4-acetamido-5-chloro-2-methoxy-N-(3-quinuclidinyl)-benzamide hydrochloride so formed precipitates (quantitative yield) and is recovered by filtration.

10

The product is subsequently deacylated by refluxing for 30 minutes in a 5% solution of potassium hydroxide in ethanol. The reaction medium is then dissolved in water and extracted with chloroform. After drying and evaporation of the organic phase, the target hydrochloride is prepared and isolated as described in Example 14.

15

Melting point: 232-234 °C  
 $[\alpha]_D^{20} = +3.8^\circ$  (c = 1, H<sub>2</sub>O)

20

COMPARISON EXAMPLE 225 S(-)-4-Amino-N-(3-quinuclidinyl)-5-chloro-2-methoxybenzamide dihydrochloride(S(-)-4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide dihydrochloride)

Following the procedure of Example 15 but using instead S(-)-3-aminoquinuclidine as prepared in Comparison Preparation 1 or 2, the corresponding S enantiomer is obtained.

30

Melting point: 233-235 °C  
 $[\alpha]_D^{20} = -3.9^\circ$  (c = 1, H<sub>2</sub>O)

35

EXAMPLE 1640 R(+)-N-(3-quinuclidinyl)benzamide hydrochloride(R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)benzamide hydrochloride)

Following the procedure of Example 14 but using benzoic acid in place of the 4-amino-5-chloro-2-methoxybenzoic acid, the title compound was prepared.

45

Melting point: 245 °C  
 $[\alpha]_D^{20} = +17.8(1, \text{CH}_3\text{OH})$

50

EXAMPLE 1755 R(+)-N-(3-quinuclidinyl)benzamide hydrochloride(R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)benzamide hydrochloride)

Following the procedure of Example 15 but using benzoyl chloride in place of the 4-amino-5-chloro-2-methoxybenzoyl chloride, the title compound was prepared.

Melting point: 245 °C

5  $[\alpha]_D^{20} = +17.8(1, \text{CH}_3\text{OH})$

#### EXAMPLE 18

10

R(+)-3-chloro-N-(3-quinuclidinyl)benzamide hydrochloride

(R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)-3-chlorobenzamide hydrochloride)

15

Following the procedure of Example 14 but using 3-chlorobenzoic acid in place of the 4-amino-5-chloro-2-methoxybenzoic acid, the title compound was prepared.

Melting point: 244 °C

20  $[\alpha]_D^{20} = +16.9(1, \text{CH}_3\text{OH})$

#### EXAMPLE 19

25

R(+)-3-chloro-N-(3-quinuclidinyl)benzamide hydrochloride

(R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)-3-chlorobenzamide hydrochloride)

30

Following the procedure of Example 15 but using 3-chlorobenzoyl chloride in place of the 4-amino-5-chloro-2-methoxybenzoyl chloride, the title compound was prepared.

Melting point: 244 °C

35  $[\alpha]_D^{20} = +16.9(1, \text{CH}_3\text{OH})$

#### EXAMPLE 20

40

R(+)-4-chloro-N-(3-quinuclidinyl)benzamide hydrochloride

(R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-chlorobenzamide hydrochloride)

45

Following the procedure of Example 14 but using 4-chlorobenzoic acid in place of the 4-amino-5-chloro-2-methoxybenzoic acid, the title compound was prepared.

Melting point: >260 °C  $[\alpha]_D^{20} = +12.5(1, \text{CH}_3\text{OH})$

50

#### EXAMPLE 21

55 R(+)-4-chloro-N-(3-quinuclidinyl)benzamide hydrochloride

(R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)-4-chlorobenzamide hydrochloride)

Following the procedure of Example 15 but using 4-chlorobenzoyl chloride in place of the 4-amino-5-chloro-2-methoxybenzoyl chloride, the title compound was prepared.

Melting point:  $>260^{\circ}\text{C}$

$[\alpha]_{\text{D}}^{20} = +12.5$  (1,  $\text{CH}_3\text{OH}$ )

#### EXAMPLE 22

R(+)-3,5-dichloro-N-(3-quinuclidinyl)benzamide hydrochloride

(R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)-3,5-dichlorobenzamide hydrochloride)

Following the procedure of Example 14 but using 3,5-dichlorobenzoic acid in place of the 4-amino-5-chloro-2-methoxybenzoic acid, the title compound was prepared.

Melting point:  $>260^{\circ}\text{C}$

$[\alpha]_{\text{D}}^{20} = +14.1$  (1,  $\text{CH}_3\text{OH}$ )

#### EXAMPLE 23

R(+)-3,5-dichloro-N-(3-quinuclidinyl)benzamide hydrochloride

(R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)-3,5-dichlorobenzamide hydrochloride)

Following the procedure of Example 15 but using 3,5-dichlorobenzoyl chloride in place of the 4-amino-5-chloro-2-methoxybenzoyl chloride, the title compound was prepared.

Melting point:  $>260^{\circ}\text{C}$

$[\alpha]_{\text{D}}^{20} = +14.1$  (1,  $\text{CH}_3\text{OH}$ )

#### PHARMACOLOGY EXAMPLE A

#### METHODOLOGY

##### Experimental Animals

Naive male albino BKW mice, 25-30g, were used in all experiments. 10 mice were normally housed in each cage and given free access to food and water. The mice were kept on a 12h light and 12h dark cycle with lights off at 8.00am and on at 8.00pm.

##### Anti-anxiety Test

The apparatus used for the detection of changes in anxiety consisted of an open topped box (45 × 27 × 27cm high) one third painted black and illuminated under a dim red light (1 × 60W) and partitioned from the remainder of the box which was painted white and brightly illuminated with a 100W light source located 17cm above the box. Access between these areas was enabled by means of a 7.5 × 7.5cm opening located at floor level in the centre of the partition. The floor area was lined into 9cm squares. The test was conducted between 13.00 and 18.00h in a quiet, darkened room illuminated with red light only. Animals were thus taken in a dark container from a dark holding room to the dark testing room.

Animals that had received drug or vehicle injections were placed individually into the centre of the white area and their behaviour observed over a 5 min period by remote video recording. Under the influence of an anxiolytic agent mice showed reduced aversion for the white, brightly lit compartment, and this was shown as Increased exploratory rearing behaviour and line crossings in the white, with corresponding reductions in the incidence of these behaviours in the black section.

#### Experimental Design

Animals were used in treatment groups of 5 and vehicle controls were run on each day of testing. Results were analysed using Single-Factor Analysis of Variance followed by Dunnett's procedure for comparing all treatments with control.

#### Drugs

Compounds of Example 14 and Comparison Example 1 were dissolved in minimum HCl made up to volume with distilled water. Doses were expressed as the base and were administered as a 40 min pretreatment in a volume of 1ml/100g body weight. Administration was by the subcutaneous route.

#### Results

Results are shown in Table 1.

TABLE 1

5	<u>Drug (mg/kg)</u>	<u>Rearings/5 min</u>	<u>Crossings/5min</u>
10	Control	<u>White Section</u>	
		22.6 $\pm$ 2.1	23.3 $\pm$ 2.1
	Ex 14      0.1	64.8 $\pm$ 6.0***	52.9 $\pm$ 5.0***
	"          1.0	82.4 $\pm$ 7.4***	87.4 $\pm$ 7.6***
15	"          10.0	76.2 $\pm$ 7.6***	73.7 $\pm$ 7.2***
	Comp Ex 1   0.1	23.0 $\pm$ 2.1	23.2 $\pm$ 2.3
	"          1.0	21.5 $\pm$ 2.0	26.8 $\pm$ 2.7
20	10.0	24.0 $\pm$ 1.9	24.7 $\pm$ 2.1
		<u>Black Section</u>	
	Control	37.5 $\pm$ 3.4	42.5 $\pm$ 4.7
25	Ex 14      0.1	13.6 $\pm$ 1.1+++	14.6 $\pm$ 1.5+++
	"          1.0	13.0 $\pm$ 1.4+++	13.6 $\pm$ 1.2+++
	"          10.0	14.7 $\pm$ 1.2+++	17.6 $\pm$ 1.4+++
30	Comp Ex 1   0.1	35.2 $\pm$ 3.1	39.4 $\pm$ 3.0
	"          1.0	38.1 $\pm$ 3.2	37.6 $\pm$ 3.8
	"          10.0	48.3 $\pm$ 4.1	50.8 $\pm$ 5.2

\*\*\*, +++ p<0.001 (two-way ANOVA followed by Dunnett's  
t test). n = 5.

#### PHARMACOLOGY EXAMPLE B

Compounds of the invention have been studied in the laboratory animal to evaluate their anxiolytic activity. As a typical compound of the invention, R(+)-4-Amino-N-(3-quinuclidinyl)-5-chloro-2-methoxy benzamide dihydrochloride (R(+)-4-Amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide dihydrochloride), the compound of Example 14, was investigated for its anxiolytic activity, which was compared with that of the racemate (unresolved product of Example 2) and the corresponding enantiomer of absolute configuration S (product of Comparison Example 1).

The method used in this example was that described by Crawley and Goodwin (Pharm. Biochem. Behavior (1980) 13, 167-170), where aspects of behaviour of the mouse are compared in a lit zone and a dark zone of a two-compartment box. The results are shown in Table 2.

**TABLE 2**  
**Exploratory Behaviour of the Mouse**

Parameters	Treatment	Dose mg/kg ip	Light zone	Dark zone
Movement activity	Control	-	23.5	42.5
	Compound of Example 2	0.1-10	+	-
	Compound of Example 14	0.1-10	+	-
	Compound of Comp. Ex.1	0.1-10	ns	ns
	Control	-	22.6	37.5
Straightenings	Compound of Example 2	0.1-10	+	-
	Compound of Example 14	0.1-10	+	-
	Compound of Comp. Ex.1	0.1-10	ns	ns

Key: + significant increase vs. control

- significant decrease vs. control

ns no significant change vs. control

It can clearly be seen that the anxiolytic activity observed after administration of a racemic mixture of a compound of the invention and its enantiomer is uniquely due to the R-enantiomer which it contains.

#### Pharmaceutical Methods and Compositions

Generally, anxiety can be controlled by means of this invention by administering internally to warm blooded animals including human beings certain R(+)-N-(1-azabicyclo[2.2.2]oct-3-yl)benzamides and thiobenzamides of Formula I, preferably Formula Ic, or a non-toxic organic or inorganic acid addition salt thereof in a wide variety of pharmaceutical forms well known in the art, preferable with a non-toxic pharmaceutical carrier such as is described below in an amount to control anxiety.

The active agent is administering orally, subcutaneously, intravenously or intramuscularly or parenterally and, if necessary, in repeated doses until satisfactory response is obtained. The daily dosage is from about 1 mcg to about 50 mg of active medication, advantageously from about 5 mcg to 5.0 mg.

The compositions may contain 5.0 mcg to 50 mg active medicament per unit dose. Preferably, the compositions contain from about 5. mcg to 50 mg of medicament, advantageously from about 5 mcg to about 5.0 mg per unit dose. The compounds may thus be presented in a therapeutic composition suitable for oral, parenteral, subcutaneous, intramuscular, intraperitoneal or intravenous administration. Thus, for example oral administration can take the form of elixirs, capsules, tablets or coated tablets containing carriers conveniently used in the pharmaceutical art. Exemplary of solid carriers including tableting and capsulating excipients are lactose, sucrose, potato and maize starches, talc, gelatin, agar, pectin or acacia, stearic and silicic acids, magnesium stearate, terra alba and polyvinyl pyrrolidone.

For parenteral administration, the carrier or excipient can be comprised of a sterile parenterally acceptable liquid; e.g., water or arachis oil contained in ampoules.

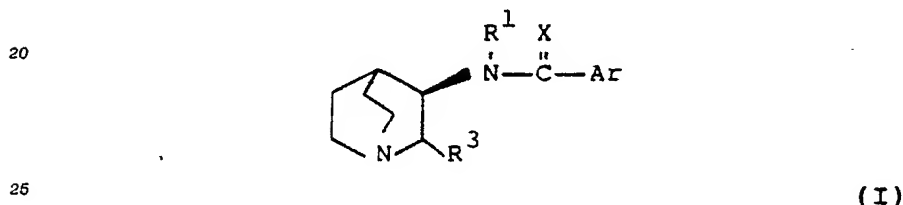
The pharmaceutical compositions may be formulated to contain from about 1.0 mcg/ml to about 50.0 mg/ml, preferably 50 mcg/ml or less. It is only necessary that the active ingredient of Formula I constitute an effective amount.

In all of the above, it is only necessary that a suitable effective dosage will be consistent with the dosage form employed. The exact individual dosages, as well as daily dosages, will of course be determined according to standard medical principles under the direction of a physician or veterinarian.

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. The invention which is intended to be protected herein, however, is not to be construed as limited to the particular forms disclosed, since these are to be regarded as illustrative rather than restrictive. Variations and changes may be made by those skilled in the art without departing from the spirit of the invention, and it is therefore understood that the invention is to be limited only by the scope of the appended claims.

# Claims

1. A compound of general formula I



wherein:

X represents oxygen or sulphur;  
each of R<sup>1</sup> and R<sup>3</sup> independently represents hydrogen or a C<sub>1</sub>-C<sub>4</sub> alkyl group;  
Ar represents:

a phenyl ring optionally substituted by one, two or three C<sub>1</sub>-C<sub>4</sub> alkoxy groups and/or by one or two halogen atoms;  
a phenyl ring of the general formula



wherein R<sup>2</sup> represents halogen, 4,5-benzo, C<sub>1</sub>-C<sub>8</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl or Am, wherein Am represents amino, methylamino or dimethylamino,  
R<sub>4</sub> represents C<sub>1</sub>-C<sub>8</sub> alkyl,  
n is 1 or 2; or  
a pyrimidinyl moiety of the general formula



wherein R<sup>5</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl;

or an N-oxide and/or pharmaceutically acceptable salt thereof.

2. A compound as claimed in claim 1, wherein each of R<sup>1</sup> and R<sup>3</sup> independently represents hydrogen, methyl or ethyl.

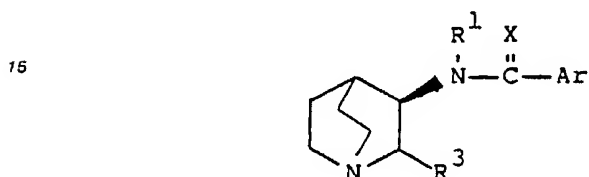
5 3. A compound as claimed in claim 1 or 2, wherein Ar represents 4-Am-5-chloro-2-methoxyphenyl.

4. R-(+)-4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide or a salt thereof.

5. A compound of general formula I as defined in claim 1, or as claimed in any one of claims 2 to 4, for use in pharmaceutical and/or veterinary medicine.

6. A pharmaceutical and/or veterinary composition comprising (a) a compound of general formula I as defined in claim 1, or as claimed in any one of claims 2 to 4, and (b) a suitable carrier therefor.

7. The use of a compound of general formula I



(I)

wherein:

25 X represents oxygen or sulphur;

each of R<sup>1</sup> and R<sup>3</sup> independently represents hydrogen or a C<sub>1</sub>-C<sub>4</sub> alkyl group;

Ar represents:

a phenyl ring optionally substituted by one, two or three C<sub>1</sub>-C<sub>4</sub> alkoxy groups and/or by one or two halogen atoms;

30 a phenyl ring of the general formula



40 wherein R<sup>2</sup> represents halogen, 4,5-benzo, C<sub>1</sub>-C<sub>8</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl or Am, wherein Am represents amino, methylamino or dimethylamino,

R<sup>4</sup> represents C<sub>1</sub>-C<sub>8</sub> alkyl,

n is 1 or 2; or

45 a pyrimidinyl moiety of the general formula



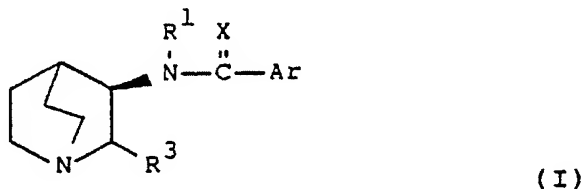
wherein R<sup>5</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl;

55 or an N-oxide and/or pharmaceutically acceptable salt thereof in the preparation of an anxiolytic agent.

8. The use of a compound as claimed claim 2 or 3 in the preparation of an anxiolytic agent.

9. The use of R-(+)-4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide or a salt thereof in the preparation of an anxiolytic agent.

10. A process for the preparation of a compound of general formula I,



wherein:

15 X represents oxygen or sulphur;

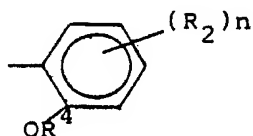
each of R<sup>1</sup> and R<sup>3</sup> independently represents hydrogen or a C<sub>1</sub>-C<sub>4</sub> alkyl group;

Ar represents:

20 a phenyl ring optionally substituted by one, two or three C<sub>1</sub>-C<sub>4</sub> alkoxy groups and/or by one or two

halogen atoms;

a phenyl ring of the general formula

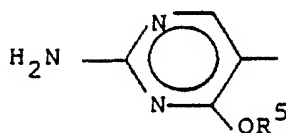


30 wherein R<sup>2</sup> represents halogen, 4,5-benzo, C<sub>1</sub>-C<sub>8</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl or Am, wherein Am represents amino, methylamino or dimethylamino,

R<sup>4</sup> represents C<sub>1</sub>-C<sub>8</sub> alkyl,

n is 1 or 2; or

a pyrimidinyl moiety of the general formula



wherein R<sup>5</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl;

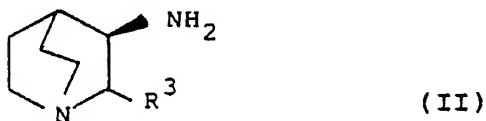
45 or an N-oxide and/or pharmaceutically acceptable salt thereof,

the process comprising either

(1) separating a compound of general formula I from a mixture with its corresponding S-enantiomer;

or

(2.1.1) coupling a 3-aminoquinuclidine of absolute configuration R of general formula (II)



wherein R<sup>3</sup> is as defined for general formula (I) with an acid of general formula (III):



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wherein Ar is as defined for general formula (I); or

(2.1.2) reacting an R-3-aminoquinuclidine of general formula (II) with an acid derivative of general formula (IIIa)

10



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wherein Ar is as defined for general formula (I) and L is a leaving group; and

(2.1.3) optionally after step 2.1.1 or 2.1.2 converting a compound of general formula (I) so formed in which X represents an oxygen atom into a compound of general formula (I) in which X represents a sulphur atom; or

20

(2.2) when X represents a sulphur atom reacting an R-3-aminoquinuclidine of general formula (II) with an aldehyde ArCHO wherein Ar is as defined for general formula (I) and sulphur; or

(2.3) for an amino-substituted compound of general formula (I) reducing a corresponding nitro-substituted compound, and

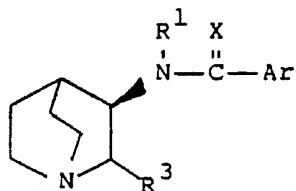
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(2.4) optionally after any of steps 1, 2.1.1, 2.1.2, 2.1.3, 2.2 and 2.3 converting a compound of general formula (I) so formed into another compound of general formula (I) or a salt thereof.

30 Claims for the following Contracting States: GR,ES

1. A compound of general formula I

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40

(I)

wherein:

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X represents oxygen or sulphur;

each of R<sup>1</sup> and R<sup>3</sup> independently represents hydrogen or a C<sub>1</sub>-C<sub>4</sub> alkyl group;

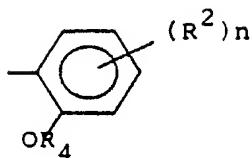
Ar represents:

a phenyl ring optionally substituted by one, two or three C<sub>1</sub>-C<sub>4</sub> alkoxy groups and/or by one or two halogen atoms;

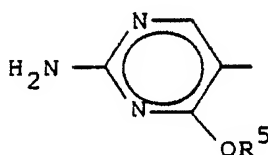
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a phenyl ring of the general formula

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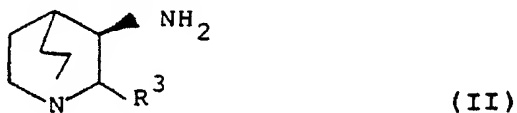
10 wherein  $R^2$  represents halogen, 4,5-benzo,  $C_1$ - $C_8$  alkoxy,  $C_1$ - $C_4$  alkylcarbonyl or Am, wherein Am represents amino, methylamino or dimethylamino,  
 $R_4$  represents  $C_1$ - $C_8$  alkyl,  
 $n$  is 1 or 2; or  
 a pyrimidinyl moiety of the general formula



wherein  $R^5$  is  $C_1$ - $C_4$  alkyl;

25 or an N-oxide and/or pharmaceutically acceptable salt thereof,  
 the process comprising either  
 (1) separating a compound of general formula I from a mixture with its corresponding S-enantiomer;  
 or  
 (2.1.1) coupling a 3-aminoquinuclidine of absolute configuration R of general formula (II)

30



wherein  $R^3$  is as defined for general formula (I) with an acid of general formula (III):



45 wherein Ar is as defined for general formula (I); or  
 (2.1.2) reacting an R-3-aminoquinuclidine of general formula (II) with an acid derivative of general formula (IIIa)



55 wherein Ar is as defined for general formula (I) and L is a leaving group; and  
 (2.1.3) optionally after step 2.1.1. or 2.1.2 converting a compound of general formula (I) so formed in which X represents an oxygen atom into a compound of general formula (I) in which X represents a sulphur atom; or

(2.2) when X represents a sulphur atom reacting an R-3-aminoquinuclidine of general formula (II) with an aldehyde ArCHO wherein Ar is as defined for general formula (I) and sulphur; or

(2.3) for an amino-substituted compound of general formula (I) reducing a corresponding nitro-substituted compound, and

5 (2.4) optionally after any of steps 1, 2.1.1, 2.1.2, 2.1.3, 2.2 and 2.3 converting a compound of general formula (I) so formed into another compound of general formula (I) or a salt thereof.

2. A process as claimed in claim 1, wherein each of R<sup>1</sup> and R<sup>3</sup> independently represents hydrogen, methyl or ethyl.

10 3. A process as claimed in claim 1 or 2, wherein Ar represents 4-Am-5-chloro-2-methoxyphenyl.

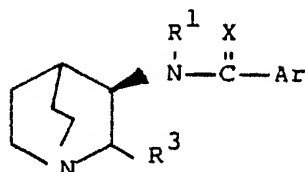
4. A process as claimed in claim 1, 2 or 3, wherein the compound of general formula I is R-(+)-4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide or a salt thereof.

5. A process for the preparation of a pharmaceutical and/or veterinary composition, the process comprising mixing (a) a compound produceable by a process as claimed in any one of claims 1 to 4, and  
15 (b) a suitable carrier therefor.

6. A process for the preparation of a pharmaceutical and/or veterinary composition, the process comprising mixing (a) R-(+)-4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide and (b) a suitable carrier therefor.

7. The use of a compound of general formula I

20



25

(I)

30

wherein:

X represents oxygen or sulphur;

each of R<sup>1</sup> and R<sup>3</sup> independently represents hydrogen or a C<sub>1</sub>-C<sub>4</sub> alkyl group;

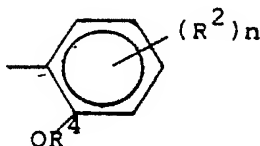
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Ar represents:

a phenyl ring optionally substituted by one, two or three C<sub>1</sub>-C<sub>4</sub> alkoxy groups and/or by one or two halogen atoms;

a phenyl ring of the general formula

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45

wherein R<sup>2</sup> represents halogen, 4,5-benzo, C<sub>1</sub>-C<sub>8</sub> alkoxy, C<sub>1</sub>-C<sub>4</sub> alkylcarbonyl or Am, wherein Am represents amino, methylamino or dimethylamino,

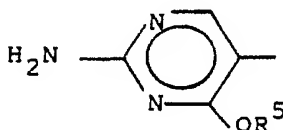
R<sup>4</sup> represents C<sub>1</sub>-C<sub>8</sub> alkyl,

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n is 1 or 2; or

a pyrimidinyl moiety of the general formula

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wherein R<sup>5</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl;

or an N-oxide and/or pharmaceutically acceptable salt thereof  
in the preparation of an anxiolytic agent.

5        8. The use of a compound as claimed in claim 2 or 3 in the preparation of an anxiolytic agent.

9. The use of R-(+)-4-amino-N-(1-azabicyclo[2.2.2]oct-3-yl)-5-chloro-2-methoxybenzamide or a salt thereof in the preparation of an anxiolytic agent.

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European Patent  
Office

# EUROPEAN SEARCH REPORT

Application Number

EP 87 40 2321

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 4)
X	WO-A-8 400 166 (SANDOZ AG) * Page 41, compound E; page 47, lines 5-10 *	1,2,5,6 ,7,8	C 07 D 453/02 A 61 K 31/435
D,X	EP-A-0 158 532 (A.H. ROBINS CO.) * Whole document *	1,2,5,6	
D,X	EP-A-0 099 789 (DELALANDE S.A.) * Whole document *	1,2,5,6	
X	EP-A-0 190 920 (A.H. ROBINS CO.) * Examples 1-3,6-8,10,11,21,24,26,34; claims *	1,2,5,6	
X	EP-A-0 237 281 (A.H. ROBINS CO.) * Whole document *	1,2,5,6	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 4)
			C 07 D 453/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 28-06-1988	Examiner VAN BIJLEN H.
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			